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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,392	05/03/2001	Vitaly Arkadievich Livshits	206440US0CONT	8292

22850 7590 10/04/2002

OBLON SPIVAK MCCLELLAND MAIER & NEUSTADT PC
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VA 22202

EXAMINER	
RAO, MANJUNATH N	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,392	LIVSHITS ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/396,357* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1, 6, 7*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 8-11 are currently pending in this application.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/396,357, filed on 9-15-1999.

Drawings

The drawings submitted in this application are accepted by the Examiner for examination purposes only.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that the figure description lacks the identification of the sequence shown in Figure 2. See particularly 37 CFR 1.821(d).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his

Claims 8-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making amino acids selected from the group consisting of L-threonine, L-homoserine, L-alanine, L-isoleucine and L-valine using a bacterium in which its resistance to L-homoserine has been enhanced by amplifying the polynucleotide encoding a protein comprising SEQ ID NO:2, or SEQ ID NO:2 in which any one single amino acid is altered, does not reasonably provide enablement for such a method using a bacterium in which resistance to L-homoserine has been enhanced by amplifying the polynucleotide encoding a protein comprising an amino acid sequence with SEQ ID NO:2 wherein one or several amino acids have been deleted, substituted, inserted or added. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 8-11 are so broad as to encompass a method of making the above amino acids using a bacterium in which resistance to L-homoserine has been enhanced by amplifying the polynucleotide encoding a protein comprising an amino acid sequence with SEQ ID NO:2 wherein one or several amino acids have been deleted, substituted, inserted or added, i.e., any

protein, --including mutants, variants, recombinants-- that provides L-homoserine resistance to said bacteria. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the method claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence with SEQ ID NO:2, that is known to impart L-homoserine resistance.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which is drawn to a method encompassing all modifications and fragments of the polypeptide with SEQ ID NO:2 because the specification does not establish: (A) regions of the protein structure (i.e., of SEQ ID NO:2) which may be modified without effecting its activity; (B) the general tolerance of the

polypeptide with SEQ ID NO:2 to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polypeptides with an enormous number of amino acid modifications of SEQ ID NO:2 used in the above method claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides or nucleotides encoding such polypeptides having the desired biological characteristics required for the methods is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 8-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 8-11 is directed to a method of making few specific amino acids using polypeptides with SEQ ID NO:2 in which one or several amino acids are deleted, substituted or inserted. Claims 8-11 are rejected under this section of 35 USC 112 because the claim is

directed to a genus of polypeptides derived from SEQ ID NO:2 including modified polypeptide sequences, modified by one or several deletions, additions, insertions and substitutions of an amino acid residue in SEQ ID NO:2 that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim in terms of its structure. No information, beyond the characterization of SEQ ID NO:2 has been provided by applicants which would indicate that they had possession of the claimed genus of modified polypeptides to perform the above method. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ ID NO:2, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structure and functions. Therefore many structurally and functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-11 are rejected under 35 U.S.C. 102(b) as anticipated by Zakataeva et al. (Abstract in 17th International Congress of Biochemistry and Molecular Biology, Aug 24-27, 1997) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Zakataeva et al. Claims 8-11 of this instant application are drawn to a method of producing L- homoserine by culturing a *E.coli* --carrying multiple copies of the gene, *rhtB* (resistance to homoserine and threonine B) encoding L-homoserine resistance protein-- and recovering the accumulated amino acid from the culture medium. Zakataeva et al. disclose the involvement of two genes *rhtA* and *rhtB* which exist in multicopy in *E.coli* and which confers resistance to amino acids homoserine and threonine. The above reference also discloses that *E.coli* carrying *rhtA* was resistant to threonine and homoserine and showed a three fold increase in the concentration of homoserine accumulated in the culture media. Zakataeva et al. also disclose that *rhtB* is present at the 86 min location near the *recQ* gene on the *E.coli* genome. However, it is not clear from the reference whether that strain of *E.coli* with a *rhtB* gene in multicopy was used for production of the amino acid threonine or homoserine. If rhtB was used for production of threonine as was rhtA, Zakataeva et al. anticipate claim 8 of the instant application. In the alternative, if *rhtB* was not in fact used for production of threonine, the above reference would have made it obvious to one

skilled in the art to culture the *E.coli* K12 strain carrying multi copies of the gene *rhtA* or *rhtB* and obtain large amounts of amino acid L-homoserine as disclosed in claim 8 of the instant application because of the value of the amino acid as a nutritive component of animal fodders as well as a reagent for pharmaceutical and chemical industry. Applicants may traverse the above rejection arguing that the reference does not provide the sequence SEQ ID NO:2 and thus the reference does not constitute a valid prior art. However, such argument will not be persuasive to overcome the above rejection because, applicants claims are now not limited to SEQ ID NO:2 or SEQ ID NO:2 in which just any one amino acid is changed, but drawn to basically any amino acid sequence which can function as a L-homoserine resistance imparting protein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zakataeva et al. (Abstract in 17th International Congress of Biochemistry and Molecular Biology, Aug 24-27, 1997) in view of Daniels et al. (Science, 1992, Vol 257: 771-778) and Debabov et al. (US 5,538,873, Jul 23, 1996). Claims 8-11 in this instant application are drawn to a method of producing L-threonine or L- homoserine by culturing a *E.coli* --carrying multiple copies of a variant gene, *rhtB* (resistance to homoserine and threonine B) encoding a variant of polypeptide SEQ ID NO:2 in which one or several amino acids are altered by way of insertion, substitution, deletion or addition and has the property of imparting L-homoserine and threonine resistance --

and recovering the accumulated amino acid from the culture medium. Zakataeva et al. teach the involvement of two genes *rhtA* and *rhtB* which exist in multicopy in *E.coli* and which confers resistance to amino acids homoserine and threonine. The above reference also teaches that the *rhtB* gene is located at 86 min region near *recQ* gene on the *E.coli* DNA and that, in culture broths of the above *E.coli* culture, there was a three fold increase in the concentration of accumulated homoserine. However, Zakataeva et al. does not teach the nucleotide sequence of the *rhtB* gene

Daniels et al. teach the nucleotide sequence of the *rhtB* gene and show that it exists in the 84.5 to 86.5 min region on the *E.coli* genome. It would have been obvious to one skilled in the art at the time the invention was made to combine the teachings of Zakataeva et al. with that of Daniels et al. to develop a method for producing large amounts of amino acid L-homoserine by subcloning the DNA sequence taught by Daniels into *E.coli* in order to increase the copy numbers of the *rhtB* gene and culture such transformed *E.coli* to allow accumulation of the amino acid L-homoserine in the culture medium. Debabov et al. teach that one would be motivated to do this as amino acids in general and L-threonine in particular is known to be an essential amino acid applicable as a nutritive component of diverse nutritive mixtures for use in animal fodders as well as a reagent for the pharmaceutical and chemical industry and also as a growth factor for microorganisms producing other amino acids such as L-lysine. One would have a reasonable expectation of success since Zakataeva et al. provide the biochemical information and the importance of this gene in the L-homoserine and L-threonine biosynthetic pathway and Daniels et al. provide the DNA sequence of the gene *rhtB*.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to have performed the claimed invention.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 8-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,303,348. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim.

See, e.g., *In re Berg*, 140 F.3d 1428,46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 is generic to all that is recited in claim 1 of US Patent No. 6,303,348. That is, claim 1 of the reference Patent fall entirely within the scope of claim 1 of the instant application or, in other words, claim 1 is anticipated by claim 1 of the reference patent. Specifically, the polypeptide of the claim 1 of the reference patent is one of the variants claimed in claim 1 of the instant application. the starting polypeptide which is used to get other polypeptides which differ at no more than 25% of the amino acid residues. Therefore the SEQ ID NO:2 and the variant comprising any one single amino acid change of claim 1 in the reference patent can be considered as one of the variant claimed in claim 1 of the instant application.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

MANJUNATH RAO
PATENT EXAMINER

Manjunath N. Rao, Ph.D.
September 27, 2002